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Risk factors for cryptorchism among populations at differing risks of testicular cancer

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Background Cryptorchism is strongly associated with the development of testicular germ cell tumours (TGCTs), possibly owing to a common aetiology. However, while TGCT incidence varies greatly between white and black men, little variability has been reported between the two groups in cryptorchism prevalence. This may suggest that cryptorchism risk factors differ by ethnicity.

Methods To examine this hypothesis, a prospective analysis was conducted among black and white participants in the US Collaborative Perinatal Project. White participants included 238 cryptorchid sons and 12 296 non-cryptorchid sons, while black participants included 188 cryptorchid sons and 11 942 non-cryptorchid sons.

Results While cryptorchism was significantly more common among white sons (1.90% vs 1.55%; $P = 0.04$), the difference was incompatible with the 5-fold difference in TGCT rates. The principal maternal risk factors among white sons were age ($P = 0.03$), hypertension/proteinuria ($P = 0.006$), and length of time to become pregnant ($P = 0.055$), while major maternal risk factors among black sons were age ($P = 0.06$), height ($P = 0.007$), weight ($P = 0.06$), and radiation exposure ($P = 0.02$). Only maternal height, however, had a different relationship with risk among black and white sons. Neonatal associations with risk (shorter gestational age, lower birthweight, shorter length) were similar in the two groups.

Conclusions These results do not support the hypothesis that the risk factors for cryptorchism vary dramatically by ethnicity but may suggest that cryptorchism is not as closely linked to TGCT among black men as among white men.

Keywords Cryptorchism, testicular cancer, ethnicity, risk factor

Cryptorchism is one of the most common congenital anomalies among males[1] and is strongly associated with the development of testicular germ cell tumours (TGCTs).[2] It has been suggested that both conditions, as well as hypospadias and poor semen quality, are part of a testicular dysgenesis syndrome (TDS) that originates *in utero*.[3] The aetiology of the TDS disorders is currently unknown, although *in utero* exposure to an oestrogenic milieu, an anti-androgenic milieu, or to placental abnormalities have all been suggested as possibilities.[4–7]

TGCTs are notable for their early age of onset (15–35 years) and for the disparity in incidence rates between different countries and different ethnic groups living in the same country. In the US, the incidence among white men, which has been increasing for at least 50 years, is five times greater than the incidence among black men.[8] This difference in TGCT rates suggests that a similar difference in the prevalence of cryptorchism may exist. It is not clear, however, that this is the case. While some studies have reported that white males have a significantly higher risk of cryptorchism than black males,[9] other studies have reported no difference in risk.[10–13] In addition, many of the suggested risk factors for cryptorchism,

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such as low birthweight, short gestational age, and being born small-for-gestational age, are reported to be more common among US black babies,[14] indicating that the relationship between these factors and cryptorchism might not be the same in white and black babies. Previous studies, however, have not specifically determined whether cryptorchism risk factors differ by ethnicity. Therefore, the present study was undertaken to examine risk factors for cryptorchism in a large, multiethnic cohort study.

Material and methods

Study participants

The study participants were enrolled in the US Collaborative Perinatal Project (CPP), a prospective study of pregnant women and the children they delivered.[15] The women were recruited between 1959 and 1965 at 12 US study centres [in Baltimore, Boston, Buffalo, Memphis, Minneapolis, New Orleans, New York (two), Philadelphia, Portland, Providence, and Richmond]. Eleven study centres recruited patients from the participating University Hospital's prenatal clinic, while one study centre recruited patients from 13 participating private practices. Women were ineligible if they were incarcerated, if they were planning to leave the area or to place the child for adoption, or if they gave birth on the day they were recruited into the study. Approximately 42 000 women were enrolled, and 55 000 children were born in the study. The children were examined at scheduled intervals for birth defects and other outcomes through age 7 years. During the first year of life, the children were assessed three times; in the delivery room, at age 4 months, and at age 12 months.

For the present study, only male babies born to black or white mothers were eligible for inclusion. Other eligibility criteria were: (i) gestation between 26 and 48 weeks, (ii) birthweight $\geqslant$500 g, and (iii) baby lived at least 1 year. Limits were placed on gestational age and birthweight because values outside the stated limits were likely to be data errors, given that the births took place in the 1960s. While gestational ages equal to or greater than 44 weeks were almost certainly inaccurate, as well, babies with those gestational ages were not excluded as it is highly likely that they were full-term.[16] As the analysis plan included gestational age only as a dichotomous variable (pre-term, not pre-term), the exclusion of babies in the 44–48 weeks gestational age range was not deemed necessary. The criterion that the children had to live at least a year was included because diagnoses of cryptorchism in the delivery room are unreliable, as testes frequently descend after birth.[17] Research indicates, however, that most testes that spontaneously descend will do so within the first 6 months of life.[18] As the CPP did not have a physical examination between the 4th and 12th months of life, however, only boys who lived until the 12 month exam were included in the current study. Boys first observed to be cryptorchid after the first year of life were not included because it was impossible, in those cases, to distinguish true cryptorchism from retractile testes.

Variables selected for evaluation included ones that were specifically maternal in nature, as well as those that were classified as neonatal. The maternal variables included age, pre-pregnancy weight, weight gain during pregnancy, height, marital status, socioeconomic status, length of time to become pregnant, gravidity, last prior pregnancy outcome, prior pregnancy loss, infertility history, blood type, Rh factor, age at menarche, DES use, all oestrogen use, progestin use, viral infections, bacterial infections, live vaccines, smoking status at enrolment, radiation exposure preceding pregnancy, hypertension/proteinuria, diabetes, hypothyroidism, hyperthyroidism, hyperemesis gravidarum, vaginal bleeding, and vomiting by trimester. One paternal variable, age of the father, was also examined. The socioeconomic index calculated for subjects in the CPP was the mean of three percentile scores (for education, occupation, and family income), where education was for the head of the household, occupation was for the head of the household or chief wage earner, and the score used to calculate the percentile for an occupation was based on the percentiles of education and income among those with the same occupation.[19]

Neonatal variables examined included gestational age, birthweight, small-for-gestational age, chest circumference, head circumference, body length, season of birth, multiple birth, method of delivery, hydramnios, inguinal hernia, hypospadias, chordee, other external abnormalities of the genitalia, genetic syndromes, and placental weight. Small-for-gestational-age was determined by comparing birthweights for each gestational age in the CPP to the 10th percentile of birthweight for gestational age developed for California non-Hispanic white births between 1970 and 1976.[20] The 10th percentiles of birthweight for gestational age for black births were obtained directly from R.L. Williams (personal communication).

Statistical methods

The proportions of unilateral and bilateral cryptorchism by ethnicity were compared using chi-squared tests of independence. For the examination of the relationship between maternal variables and cryptorchism, race-specific univariate logistic regression analyses were used to compute relative risks (RRs) and 95% confidence intervals (95% CIs) for each variable. For these analyses, most continuous variables were categorized based on their distribution in the whole study population. In the next step, race-specific multivariable logistic regression models of maternal variables that included variables found to be statistically significant in the univariate analyses were examined. Next, a multivariable logistic regression model that included the maternal variables from both the black and white analyses was examined. The model also included a term for race. Finally, a series of multivariable logistic regression models were examined that included interaction terms between race and each maternal variable.

The same analysis strategy was repeated for the neonatal variables. Race-specific univariate models identified neonatal factors related to cryptorchism. Significant factors were then included in race-specific multivariable models. Finally, all neonatal data were included in a single model that included a term for race and, as a last step, the significance of interactions between race and each variable were examined in a series of models. Although the interpretation of such a model is not entirely clear, a final analysis included all variables, both neonatal and maternal, in a single model. All statistical tests were two-sided. Analyses were done using the SAS software package, version 8.0 (SAS Institute, Cary, NC).

Results

Data from 24 664 male births were included in the analysis. 12 534 of the births (50.8%) occurred among white mothers and 12 130 (49.2%) occurred among black mothers. Among the sons of white mothers, there were 238 diagnoses of cryptorchism, resulting in a prevalence of 1.90%. The comparable prevalence among sons of black mothers, 1.55% (188/12 130), was significantly lower than the prevalence among the white sons ($\chi^2 = 4.42$; $P = 0.04$). Among the sons with cryptorchism, 31% (74/238) of the white sons had bilateral cryptorchism, compared with 24% (45/188) of the black sons; a difference that was not statistically significant ($\chi^2 = 2.67$; $P = 0.10$).

White and black mothers of cryptorchid sons were similar to mothers of non-cryptorchid sons with respect to maternal weight gain, marital status, socioeconomic status, smoking status at study enrolment, infertility history, gravidity/parity, prior pregnancy loss, last prior pregnancy outcome, diabetes, hyperemesis gravidarum, and DES use (Table 1). Case and control mothers also did not vary with respect to body mass index, blood type, Rh factor, history of dysmenorrhoea, age at menarche, any oestrogen use in pregnancy, progestin use in pregnancy, viral or bacterial infections, live vaccines received, hypothyroidism, hyperthyroidism, vaginal bleeding during pregnancy, vomiting during pregnancy, or having a previous child with a congenital malformation (data not shown).

Among white mothers, variables significantly related to cryptorchism included older maternal age, longer duration of time trying to become pregnant, and gestational hypertension or pre-eclampsia (Table 1). Risk also increased with increasing paternal age, although the risk was not significant until the father's age reached 40 years (RR = 5.4; 95% CI 1.3–23.4). Among black mothers, height and radiation exposure were significantly associated with risk. Black mothers' risk also increased directly with age ($P = 0.06$) and weight ($P = 0.06$).

A multivariable analysis of the maternal risk factors that were univariately related to risk found that only older maternal age ($P = 0.02$) and hypertension/proteinuria ($P = 0.002$) remained significant among white mothers (Table 2). Among black mothers, only maternal height ($P = 0.002$) remained significantly associated with risk, while radiation in the previous 12 months remained of borderline significance ($P = 0.054$). The inclusion of medical centre into the models had no effect on the results.

An examination of maternal variables in a single model that included the data of all mothers found that the only variable that remained significantly related to cryptorchism was hypertension/proteinuria ($P = 0.04$). The subsequent series of models that included interaction terms between race and each maternal variable found that only height had a different relationship to cryptorchism in blacks and whites ($P = 0.02$). While the black mothers had a U-shaped relationship between risk and height, there was no indication of any relationship among white mothers.

Neonatal variables that were significantly associated with risk among both black and white babies included lower birthweight, shorter body length, and smaller chest circumference (Table 3). Inguinal hernia, hypospadias, other external urogenital anomalies, and genetic syndromes were also significantly associated with risk in both ethnic groups. Among black babies, smaller head circumference (RR = 0.9; 95% CI 0.8–0.9) and placental weight (data not shown) were significantly associated with risk, while among white babies, hydramnios (RR = 2.1; 95% CI 1.1–3.9) and chordee (RR = 8.7; 95% CI 1.9–39.4) were significantly associated. Neither decreased gestational age (<37 weeks) nor being born small-for-gestational-age were formally associated with risk although decreased gestational age was of borderline significance ($P = 0.055$) in white babies, while being small-for-gestational-age was of borderline significance ($P = 0.08$) in black babies.

Among white babies, a multivariable analysis of the neonatal factors that were univariately associated with risk found that only low birthweight ($P = 0.0005$) remained significantly related to risk (Table 4). Shorter body length was related to risk, though the association was only of marginal significance ($P = 0.06$). Similarly, among black babies only low birthweight remained significantly associated with risk ($P = 0.0003$). The inclusion of medical centre into models did not affect the results. For both analyses of black and white babies, identical results were obtained whether forward or backward stepwise logistic regression was employed.

In a final examination of the data, both maternal and neonatal variables were examined together in a single model. In a model that included the data of all mothers and sons, only maternal weight ($P = 0.02$), birthweight ($P = 0.001$), and race ($P = 0.006$) were significantly associated with risk of cryptorchism. The subsequent series of models that included interaction terms between race and each variable found that, again, only height had a different relationship with cryptorchism in blacks and whites ($P = 0.01$).

Discussion

One of the most striking features of TGCT is the great difference in risk among various ethnic groups.[8] As cryptorchism is one of the few well-established TGCT risk factors, it might be expected that the prevalence of cryptorchism would show a similar disparity. Most studies, however, have not reported a substantial difference in risk.[10–12,21]

One report to find a significantly higher prevalence of cryptorchism among white babies originated from the CPP.[9] Defining cryptorchism differently than in the present study, the report noted that the prevalence among white babies was three times the prevalence among black babies. However, the findings were based on only 12 diagnoses of cryptorchism; nine among white and three among black babies. In contrast, three other reports from the CPP, using various definitions of cryptorchism, found no difference in prevalence by ethnicity,[10,11,21] though one study did note a higher prevalence of bilateral cryptorchism among white (0.23%) vs black babies (0.15%).[10] Studies of other US populations have not found a significant difference in prevalence between the two groups.[12,13]

The present study's finding of a significantly higher prevalence of cryptorchism among white sons is not inconsistent with these prior reports, given that the white prevalence

Table 1 Univariate association between maternal variables and cryptorchism among white and black mothers in the Collaborative Perinatal Project

	White mothers				Black mothers			
Variable	Cases [*n* (%)] (*n* = 238)	Controls [*n* (%)] (*n* = 12 296)	RR (95% CI)	Global *P*-value	Cases [*n* (%)] (*n* = 188)	Controls [*n* (%)] (*n* = 11 942)	RR (95% CI)	Global *P*-value
Maternal age (years)				0.03				0.06
<20	30 (12.6)	2185 (17.8)	1.0		43 (22.9)	3482 (29.2)	1.0	
20–29	146 (61.3)	7668 (62.4)	1.4 (0.9–2.1)		101 (53.7)	6334 (53.0)	1.3 (0.9–1.9)	
30–39	55 (23.1)	2235 (18.2)	1.8 (1.1–2.8)		38 (20.2)	1939 (16.2)	1.6 (1.0–2.5)	
40+	7 (2.9)	208 (1.7)	2.5 (1.1–5.7)		6 (3.2)	187 (1.6)	2.6 (1.1–6.2)	
Maternal weight (lbs)[a]				0.68				0.06
<118	72 (30.3)	3956 (32.2)	1.0		43 (22.9)	3602 (30.2)	1.0	
118–134	77 (32.4)	4048 (32.9)	1.0 (0.8–1.4)		52 (27.7)	3365 (28.2)	1.3 (0.9–1.9)	
⩾135	82 (34.5)	3918 (31.9)	1.2 (0.8–1.6)		86 (45.7)	4646 (38.9)	1.6 (1.1–2.2)	
Unknown	7 (2.9)	374 (3.0)			7 (3.7)	329 (2.8)		
Maternal weight gain (lbs)				0.48				0.30
<17	66 (27.7)	2965 (24.1)	1.0		57 (30.3)	3308 (27.7)	1.0	
17–24	79 (33.2)	4121 (33.5)	0.9 (0.6–1.2)		42 (22.3)	3337 (27.9)	0.7 (0.5–1.1)	
⩾25	76 (31.9)	4166 (33.9)	0.8 (0.6–1.1)		64 (34.0)	4114 (34.5)	0.9 (0.6–1.3)	
Unknown	17 (7.1)	1044 (8.5)			25 (13.3)	1183 (9.9)		
Maternal height (inches)				0.83				0.007
<62	43 (18.1)	2139 (17.4)	1.0		43 (22.9)	2338 (19.6)	1.0	
62–64	91 (38.2)	4778 (38.9)	0.9 (0.7–1.4)		62 (33.0)	5396 (45.2)	0.6 (0.4–0.9)	
⩾65	72 (30.3)	4019 (32.7)	0.9 (0.6–1.3)		73 (38.8)	3796 (31.8)	1.1 (0.7–1.5)	
Unknown	32 (13.5)	1360 (11.1)			10 (5.3)	412 (3.5)		
Paternal age (years)				0.12				0.13
<20	2 (0.8)	393 (3.2)	1.0		4 (2.1)	359 (3.0)	1.0	
20–29	130 (54.6)	6419 (52.2)	3.9 (0.9–16.1)		60 (31.9)	4434 (37.1)	1.2 (0.4–3.4)	
30–39	57 (24.0)	2978 (24.2)	3.8 (0.9–15.5)		41 (21.8)	2064 (17.3)	1.8 (0.6–5.0)	
40+	20 (8.4)	723 (5.9)	5.4 (1.3–23.4)		15 (8.0)	666 (5.6)	2.0 (0.7–6.1)	
Unknown	29 (12.2)	1783 (14.5)			68 (36.2)	4419 (37.0)		
Marital status				0.50				0.89
Single	7 (2.9)	558 (4.5)	1.0		46 (24.5)	3110 (26.0)	1.0	
Married	214 (89.9)	10 902(88.7)	1.6 (0.3–3.3)		123 (65.4)	7658 (64.1)	1.1 (0.8–1.5)	
Separated/widowed/divorced	17 (7.1)	835 (6.8)	1.6 (0.7–3.9)		19 (10.1)	1174 (9.8)	1.1 (0.6–1.9)	
Unknown	0 (0.0)	1 (0.01)			0 (0.0)	0 (0.0)		
Socioeconomic index				0.19				0.84
<37	47 (19.8)	2159 (17.6)	1.0		83 (44.2)	5370 (45.0)	1.0	
37–56	77 (32.4)	3463 (28.2)	1.0 (0.7–1.5)		68 (36.2)	4322 (36.2)	1.0 (0.7–1.4)	
⩾57	109 (45.8)	6299 (51.2)	0.8 (0.6–1.1)		36 (19.2)	2069 (17.3)	1.1 (0.8–1.7)	
Unknown	5 (2.1)	375 (3.1)			1 (0.5)	181 (1.5)		
Smoking status[b]				0.43				0.20
Non-smoker	116 (48.7)	5637 (45.8)	1.0		100 (53.2)	6879(57.6)	1.0	
Smoker	121 (50.8)	6518 (53.0)	0.0 (0.7–1.2)		87 (46.3)	4960 (41.5)	1.2 (0.9–1.6)	
Unknown	1 (0.4)	141 (1.1)			1 (0.5)	103 (0.9)		
Infertility history				0.55				0.92
No	233 (97.9)	12 024(97.8)	1.0		187 (99.5)	11 763 (98.5)	1.0	
Yes	5 (2.1)	197 (1.6)	1.3 (0.5–3.2)		1 (0.5)	70 (0.6)	0.9 (0.1–6.5)	
Unknown	0 (0.0)	75 (0.6)			0 (0.0)	109 (0.9)		

Table 1 *Continued*

Variable	White mothers				Black mothers			
	Cases [*n* (%)] (*n* = 238)	Controls [*n* (%)] (*n* = 12 296)	RR (95% CI)	Global *P*-value	Cases [*n* (%)] (*n* = 188)	Controls [*n* (%)] (*n* = 11 942)	RR (95% CI)	Global *P*-value
Radiation 12 months before								
None	104 (43.7)	5620 (45.7)	1.0	0.60	91 (48.4)	6016 (50.4)	1.0	0.02
Abdomino-pelvic	18 (7.6)	770 (6.53)	1.3 (1.0–3.6)		15 (8.0)	454 (3.8)	2.2 (1.3–3.8)	
Other areas only	114 (47.9)	5618 (45.7)	1.1 (0.8–1.4)		80 (42.6)	5268 (44.1)	1.0 (0.7–1.4)	
Unknown	2 (0.8)	288 (2.3)			2 (1.1)	204 (1.7)		
Time to pregnancy (months)				0.055				0.97
Not trying	170 (71.4)	9223 (75.0)	1.0		175 (93.1)	11 047(92.5)	1.0	
⩽12	51 (21.4)	2334 (19.0)	1.2 (0.9–1.6)		9 (4.8)	615 (5.2)	0.9 (0.5–1.8)	
>12	13 (5.5)	362 (2.9)	2.0 (1.1–3.5)		2 (1.1)	117 (1.0)	1.1 (0.3–4.6)	
Unknown	4 (1.7)	377 (3.1)			2 (1.1)	163 (1.4)		
Prior pregnancies				0.48				0.73
None	63 (26.5)	3675 (29.9)	1.0		45 (23.9)	3096 (25.9)	1.0	
Pregnant but no live birth	5 (2.1)	284 (2.3)	1.0 (0.4–2.6)		0 (0.0)	241 (2.0)		
Live births	170 (71.4)	8298 (67.5)	1.2 (0.9–1.6)		143 (76.1)	8578 (71.8)	1.2 (0.8–1.6)	
Unknown	0 (0.0)	39 (0.3)			0 (0.0)	27 (0.2)		
Last prior outcome				0.60				0.82
No prior outcome	63 (26.5)	3675 (29.9)	1.0		45 (23.9)	3096 (25.9)	1.0	
Fetal death	26 (10.9)	1169 (9.5)	1.3 (0.8–2.2)		17 (9.0)	1256 (10.5)	0.9 (0.5–1.6)	
Child died	5 (2.1)	208 (1.7)	1.4 (0.6–3.5)		6 (3.2)	324 (2.7)	1.3 (0.5–3.0)	
Child still living	142 (59.7)	7013 (57.0)	1.2 (0.9–1.6)		114 (60.6)	7028 (58.9)	1.1 (0.8–1.6)	
Unknown	2 (0.8)	231 (1.9)			6 (3.2)	238 (2.0)		
Prior pregnancy loss				0.25				0.51
None	120 (50.4)	6183 (50.3)	1.0		95 (50.5)	6068 (50.8)	1.0	
1 or more	51 (21.4)	2152 (17.5)	1.2 (0.9–1.7)		47 (25.0)	2559 (21.4)	1.2 (0.8–1.7)	
No prior pregnancy	64 (26.9)	3695 (30.1)	0.9 (0.7–1.2)		45 (23.9)	3106 (26.0)	0.9 (0.7–1.3)	
Unknown	3 (1.3)	266 (2.2)			1 (0.5)	209 (1.8)		
Hypertension/proteinuria				0.006				0.70
None	171 (71.9)	9641 (78.4)	1.0		137 (72.9)	8398 (70.3)	1.0	
Gestational hypertension	27 (11.3)	948 (7.7)	1.6 (1.1–2.4)		20 (10.6)	1140 (9.6)	1.1 (0.7–1.7)	
Gestational proteinuria	2 (0.8)	39 (0.3)	2.9 (0.7–12.1)		1 (0.5)	77 (0.6)	0.8 (0.1–5.8)	
Gestational hypertension or gestational proteinuria before 24 weeks	0 (0.0)	18 (0.2)			0 (0.0)	22 (0.2)		
Chronic hypertension	25 (10.5)	1317 (10.7)	1.1 (0.7–1.6)		22 (11.7)	1876 (15.7)	0.7 (0.5–1.1)	
Pre-eclampsia/eclampsia	12 (5.0)	252 (2.1)	2.7 (1.5–4.9)		8 (4.3)	377 (3.2)	1.3 (0.6–2.7)	
Unknown	1 (0.4)	81 (0.7)			0 (0.0)	52 (0.4)		
Diabetes				0.91				0.48
No	232 (97.5)	11 958(97.3)	1.0		187 (99.5)	11 740(98.3)	1.0	
Yes	6 (2.5)	295 (2.4)	1.1 (0.5–2.4)		1 (0.5)	128 (1.1)	0.5 (0.1–3.5)	
Unknown	0 (0.0)	43 (0.4)			0 (0.0)	74 (0.6)		
Hyperemesis gravidarum				0.89				0.47
No	234 (98.3)	11 974 (97.4)	1.0		186 (98.9)	11 745(98.4)	1.0	
Yes	4 (1.7)	191 (1.6)	1.1 (0.4–2.9)		2 (1.1)	75 (0.6)	1.7 (0.4–6.9)	
Unknown	0 (0.0)	131 (1.1)			0 (0.0)	122 (1.0)		
DES use				0.23				0.28
No	235	12 219	1.0		187	11 921	1.0	
Yes	3	77	2.0 (0.6–6.5)		1	21	3.0 (0.4–22.7)	

[a] Pre-pregnant weight.
[b] Smoking status at study enrolment.

Table 2 Multivariate models of the association between maternal variables and cryptorchism among mothers in the Collaborative Perinatal Project

	RR	(95% CI)	*P*-value[a]
White mothers (233 cases, 11 861 controls)			
Maternal age (years)			0.02
<20	1.0		
20–29	1.5	(1.0–2.2)	
30–39	1.9	(1.2–3.0)	
40+	2.6	(1.1–6.1)	
Hypertension/proteinuria			0.002
None	1.00		
Gestational proteinuria	3.0	(0.7–12.7)	
Gestational hypertension	1.7	(1.1–2.6)	
Chronic hypertension	1.0	(0.7–1.6)	
Pre-eclampsia/eclampsia	3.0	(1.6–5.4)	
Time to Pregnancy[b]			0.17
Black mothers (184 cases, 11 934 controls)			
Maternal height (inches)			0.002
<62	1.0		
62–64	0.6	(0.4–0.9)	
≥65	1.0	(0.7–1.5)	
Maternal age (years)[b]			0.59
Radiation 12 months before[b]			0.054
Maternal weight (lbs)[b,c]			0.17

[a] *P*-values computed by backwards stepwise logistic regression.
[b] No risk estimate is provided as variable was not included in final model.
[c] Pre-pregnant weight.

(1.90%) is less than half a per cent higher than the black prevalence (1.55%). Such a small degree of difference cannot explain the 5-fold difference in TGCT incidence but may suggest that cryptorchism is not as closely linked to TGCT among black men. However, few data currently exist on the cryptorchism–TGCT relationship in black men, as most TGCT studies have been unable to include black participants. One study from South Africa, however, found that cryptorchism was significantly more common among black TGCT patients than among white.[22] This finding is consistent with the alternative hypothesis that the cryptorchism-TGCT link is similar in both groups, but there are other unidentified risk factors that are more common among white populations. It is also possible that the higher risk among white populations is due to increased genetic susceptibility to an exposure equally common among blacks and whites.

In the current study, an examination of cryptorchism risk factors in black and white sons found no striking differences between the groups. The only factor that had a different relationship with risk by ethnicity was maternal height. Among black mothers, height was the single factor most significantly related to cryptorchism and had a U-shaped association with risk such that mothers shorter than 5′2″ or taller than 5′4″ had an increased risk. Though height has not been extensively examined in prior studies, one other study found a similar U-shaped association,[7] and several studies reported body mass index associations with risk.[11,12] In the present study, however, the association between weight and risk in black mothers disappeared when weight was examined in a multivariate model with height. When weight and height were replaced in the model with body mass index, there was no association with risk. Why height of black mothers would increase risk at the ends of the spectrum in not clear but is not likely explained by maternal hormones levels. In a companion study to the present one, height of black mothers was not associated with estradiol, estriol, or testosterone levels in either first or third trimester samples.[23] As height was one of many variables examined in the current study, it is also possible that the association was a chance finding.

Other than that for maternal height, there were no significant differences in the distributions of the variables among the black and white participants. Among white mothers, but not black mothers, increased maternal age, a longer time trying to become pregnant, and increased risk among older primigravidas suggest that subfertility might be related to risk. Whether subfertility was more common among the white mothers is unclear, although the white mothers were slightly older than the black mothers and were more likely to be primigravidas. In addition, white mothers were more than twice as likely as black mothers to have a history of infertility (3.63% vs 1.29%). Prior studies of white mothers have also reported an association between cryptorchism and decreased fertility.[7,24,25] Further speculation based on the current study is somewhat difficult, however, as the study did not ascertain whether any underlying subfertility was maternal or paternal in nature.

Another possible explanation for the maternal age association in white mothers is that some studies have found that maternal estradiol[26,27] and testosterone levels decline[23,26] with age, though other studies have reported no association.[28] In a CPP companion study to the present one, estradiol was not associated with age in either white or black mothers.[23] In white mothers, however, a significant inverse association was found between testosterone levels and age, suggesting that the lower testosterone levels of older white mothers increase the risk of cryptorchism in their sons. This hypothesis was not supported in another companion CPP study, however, which found no relationship between maternal testosterone levels and cryptorchism in either white or black mothers.[29]

Similar to the maternal factors, associations between neonatal factors and cryptorchism did not vary greatly between black and white babies. Gestational age was more strongly associated with cryptorchism among white babies, while being small-for-gestational-age was more strongly associated in black babies. Neither variable, however, was formally significant. The lack of significance may have been due to the exclusion criteria, which limited study participation by length of gestation, birthweight, and vital status at 1 year.

Most measures of size of the baby (birthweight, chest circumference, and body length) were significantly related to risk among all babies, such that smaller, lighter babies were at higher risk than larger, heavier babies. Although the associations between body length and chest circumference with risk

Table 3 Univariate association between neonatal variables and cryptorchism among white and black neonates in the Collaborative Perinatal Project

	White babies				Black babies			
	Cases [*n* (%)] (*n* = 238)	Controls [*n* (%)] (*n* = 12 296)	RR (95% CI)	Global *P*-value	Cases [*n* (%)] (*n* = 188)	Controls [*n* (%)] (*n* = 11 942)	RR (95% CI)	Global *P*-value
Gestation length (weeks)				0.055				0.12
<37	33 (13.9)	1236 (10.1)	1.4 (1.0–2.1)		49 (26.1)	2548 (21.3)	1.3 (0.9–1.8)	
⩾37	205 (86.1)	11 060 (90.0)	1.0		139 (73.9)	9394 (78.7)	1.0	
Birthweight (g)				0.001				<0.001
500–2499	29 (12.2)	758 (6.2)	2.1 (1.4–3.2)		39 (20.7)	1343 (11.3)	2.0 (1.4–2.9)	
2500–3999	188 (79.0)	10 76 (84.4)	1.0		144 (76.6)	10 19 (84.7)	1.0	
4000+	21 (8.8)	1162 (9.5)	1.0 (0.6–1.6)		5 (2.7)	480 (4.0)	0.7 (0.3–1.8)	
Small-for-gestational-age				0.22				0.08
No	203 (85.3)	10 08 (87.9)	1.0		160 (85.1)	10 640 (89.1)	1.0	
Yes	35 (14.7)	1488 (12.1)	1.3 (0.9–1.8)		28 (14.9)	1302 (10.9)	1.4 (1.0–2.2)	
Chest circumference (cm)				0.005				<0.001
Mean (SD)	31.97 (2.71)	32.4 (2.18)	0.9 (0.9–1.0)		30.92 (2.89)	31.57 (2.24)	0.9 (0.8–1.0)	
Head circumference (cm)				0.08				<0.001
Mean (SD)	34.06 (1.60)	34.24 (1.55)	0.9 (0.9–1.0)		33.26 (2.04)	33.68 (1.65)	0.9 (0.8–0.9)	
Body length (cm)				<0.008				0.004
<49	52 (21.9)	1997 (16.2)	1.6 (1.1–2.2)		72 (38.3)	3332 (27.9)	1.6 (1.2–2.3)	
49–50	77 (32.4)	3299 (26.8)	1.4 (1.1–1.9)		47 (25.0)	3730 (31.2)	1.0 (0.7–1.4)	
>50	107 (45.0)	6557 (53.3)	1.0		62 (33.0)	4652 (39.0)	1.0	
Unknown	2 (0.8)	443 (3.6)			7 (3.7)	228 (1.9)		
Season of birth				0.52				0.42
Winter	57 (24.0)	2965 (24.1)	1.0		43 (22.9)	2906 (24.3)	1.0	
Spring	54 (22.7)	3058 (24.9)	0.9 (0.7–1.3)		52 (27.7)	2685 (22.5)	1.3 (0.9–2.0)	
Summer	59 (24.8)	3256 (26.5)	0.9 (0.7–1.4)		47 (25.0)	3212 (26.9)	1.0 (0.7–1.5)	
Fall	68 (28.6)	3017 (24.5)	1.2 (0.8–1.7)		46 (24.5)	3139 (26.3)	1.0 (0.7–1.5)	
Inguinal hernia				<0.0001				<0.0001
No	199 (83.6)	11 810 (96.1)	1.0		162 (86.2)	11 514 (96.4)	1.0	
Yes	39 (16.4)	486 (4.0)	4.8 (3.3–6.8)		26 (13.8)	428 (3.6)	4.3 (2.8–6.6)	
Hypospadias				<0.0001				0.0005
No	227 (95.4)	11 121 (90.4)	1.0		180 (95.7)	11 217 (93.9)	1.0	
Yes	9 (3.8)	71 (0.6)	6.2 (3.1–12.6)		5 (2.7)	60 (0.5)	5.2 (2.1–13.1)	
Unknown	2 (0.8)	1104 (9.0)			3 (1.6)	665 (5.6)		
Chordee				0.005				0.98
No	234 (98.3)	11 181 (90.9)	1.0		185 (98.4)	11 271 (94.4)	1.0	
Yes	2 (0.8)	11 (0.1)	8.7 (1.9–39.4)		0 (0.0)	6 (0.1)		
Unknown	2 (0.8)	1104 (9.0)			3 (1.6)	665 (5.6)		
External genitalia abnormality				<0.0001				<0.0001
No	224 (94.1)	11 154 (90.7)	1.0		178 (94.7)	11 235 (94.1)	1.0	
Yes	12 (5.0)	38 (0.3)	15.7 (8.1–30.5)		7 (3.7)	42 (0.4)	10.5 (4.7–23.7)	
Unknown	2 (0.8)	1104 (9.0)			3 (1.6)	665 (5.6)		
Genetic syndrome				0.02				0.03
No	235 (98.7)	12 258 (99.7)	1.0		186 (98.9)	11 916 (99.8)	1.0	
Yes	3 (1.3)	38 (0.3)	4.1 (1.3–13.4)		2 (1.1)	26 (0.2)	4.9 (1.2–20.9)	
Multiple birth				0.31				0.09
Singleton	232 (97.5)	12 092 (98.3)	1.0		181 (96.3)	11 707 (98.0)	1.0	
Multiple	6 (2.5)	204 (1.7)	1. 5 (0.7–3.5)		7 (3.7)	235 (2.0)	1.9 (0.9–4.2)	

Table 3 *Continued*

	White babies				Black babies			
	Cases [*n* (%)] (*n* = 238)	Controls [*n* (%)] (*n* = 12 296)	RR (95% CI)	Global *P*-value	Cases [*n* (%)] (*n* = 188)	Controls [*n* (%)] (*n* = 11 942)	RR (95% CI)	Global *P*-value
Method of delivery				0.49				0.11
Vertex	213 (89.5)	11 135 (90.6)	1.0		167 (88.8)	11 034 (92.4)	1.0	
Breech	10 (4.2)	357 (2.9)	1.5 (0.8–2.8)		7 (3.7)	254 (2.1)	1.8 (0.9–3.9)	
C-section	15 (6.3)	712 (5.8)	1.1 (0.7–1.9)		14 (7.5)	602 (5.1)	1.5 (0.9–2.7)	
Unknown	0 (0.0)	90 (0.7)			0 (0.0)	52 (0.4)		
Hydramnios				0.02				0.34
No	227 (95.4)	11 891 (96.7)	1.0		184 (97.9)	11 664 (97.7)	1.0	
Yes	11 (4.6)	274 (2.2)	2.1 (1.1–3.9)		4 (2.1)	156 (1.3)	1.6 (0.6–4.4)	
Unknown	0 (0.0)	131 (1.1)			0 (0.0)	122 (1.0)		

Table 4 Multivariate models of the association between neonatal/placental variables and cryptorchism among black and white babies in the Collaborative Perinatal Project

	White babies (233 cases, 12 994 controls)			Black babies (181 cases, 11 934 controls)		
	RR	(95% CI)	*P*-value[a]	RR	(95% CI)	*P*-value[a]
Birthweight (g)			0.007			0.0003
500–2499	2.2	(1.5–3.2)		2.1	(1.5–3.0)	
2500–3999	1.0			1.0		
4000+	1.0	(0.7–1.6)		0.8	(0.3–1.9)	
Body length (in tertiles)[b]			0.06			0.28
Gestation length (weeks)[b]			0.64			0.82

[a] *P*-values computed by backwards stepwise logistic regression.
[b] No risk estimate is provided as variable was not included in final model.

have not been widely examined in prior studies, their association with risk is not surprising given their relationship with birthweight and gestational age. Other genitourinary anomalies, such as inguinal hernia, hypospadias, and abnormalities of the genitalia were also, as anticipated from prior studies, significantly related to risk among all babies.[7,12,13,24,30,31]

Taken as a whole, the current study suggests that there are few differences in risk factors for cryptorchism among white and black babies. The relationship with maternal age in both white and black mothers and with time-to-pregnancy in white mothers may indicate that some aspect of maternal subfertility is related to cryptorchism. If this is the case, it might be expected that the prevalence of cryptorchism would have increased somewhat in the last 40 years as average maternal age has increased during this interval.[14] Recent reports, however, have not found an increase in cryptorchism prevalence in the US though time trends have been difficult to estimate given temporal changes in definition.[32] In support of the relationship between cryptorchism and maternal age are other recent reports that another TDS congenital disorder, hypospadias, also appears to be associated with maternal age.[33–35]

The major strengths of the current study were the prospective nature and focus on examination of the children over a number of years. This is an important consideration as full testicular descent is a late event in pregnancy, often not being completed until well after birth . The study was also quite large, including almost 25 000 births, was comprised of almost equal numbers of black and white babies, and included more black babies than any previously reported study. Although prior studies have included more than one ethnic group, most have not specifically examined whether there were differences in risk factors by ethnicity.

Given the size of the study, there was more than sufficient power to detect significant differences, even small differences that might contribute little to total risk. In that the study confirmed many previously reported associations, however, it is unlikely that the currently reported risk factors achieved significance only as a result of large numbers. The study also examined association with a large number of variables, which might increase the likelihood of finding statistically significant results. As a result, the findings were interpreted cautiously. Similarly, while the prospective nature of the study was an ideal design, it limited the number of cryptorchid cases that could be examined. Finally, the fact that the study took place in the 1960s may limit the ability to extrapolate findings to the present time.

In conclusion, the small difference in cryptorchism prevalence and the negligible differences in cryptorchism risk factors suggest that neither cryptorchism nor cryptorchism risk factors determine the difference in TGCT incidence among black and white men. Other, as yet, unidentified factors may be present among white populations, but not among black populations. It is difficult to know what these other factors might be as very few TGCT studies have included black men. Future efforts to include ethnic minorities in TGCT studies may prove helpful in elucidating why the rates vary greatly among different populations of men.

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KEY MESSAGES

- In the US Collaborative Perinatal Project, the prevalence of cryptorchism, a risk factor for testicular cancer, was 1.90% among white sons and 1.55% among black sons.
- Risk factors for cryptorchism did not vary greatly between white and black sons.
- Given that testicular cancer rates are significantly higher among white men, these data suggest that cryptorchism may not be as closely linked to testicular cancer in black men as in white men.

References

[1] John Radcliffe Hospital Cryptorchidism Study Group. Cryptorchidism: a prospective study of 7500 consecutive male births, 1984-8. *Arch Dis Child* 1992;**67:**892–99.

[2] McGlynn KA. Environmental and host factors in testicular germ cell tumors. *Cancer Invest* 2001;**19:**842–53.

[3] Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;**16:**972–78.

[4] Henderson BE, Bernstein L, Ross RK, Depue RH, Judd HL. The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer* 1988;**57:** 216–18.

[5] Henderson BE, Ross RK, Pike MC, Depue RH. Epidemiology of testis cancer. In: Skinner D (ed.). *Urological Cancer*. New York: Grune & Stratton, 1983, p. 237.

[6] Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993;**341:**1392–95.

[7] Akre O, Lipworth L, Cnattingius S, Sparen P, Ekbom A. Risk factor patterns for cryptorchidism and hypospadias. *Epidemiology* 1999;**10:** 364–69.

[8] McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer* 2003;**97:**63–70.

[9] Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Boston, MA: John Wright PSG Inc., 1977.

[10] Myrianthopoulos NC, Chung CS. Congenital malformations in singletons: epidemiologic survey. Report from the Collaborative Perinatal project. *Birth Defects Orig Artic Ser* 1974;**10:**1–58.

[11] Depue RH. Maternal and gestational factors affecting the risk of cryptorchidism and inguinal hernia. *Int J Epidemiol* 1984;**13:**311–18.

[12] Berkowitz GS, Lapinski RH, Godbold JH, Dolgin SE, Holzman IR. Maternal and neonatal risk factors for cryptorchidism. *Epidemiology* 1995;**6:**127–31.

[13] Biggs ML, Baer A, Critchlow CW. Maternal, delivery, and perinatal characteristics associated with cryptorchidism: a population-based case–control study among births in Washington State. *Epidemiology* 2002;**13:**197–204.

[14] Hamilton BE, Martin JA, Sutton PD. Births: preliminary data for 2003. *National Vital Statistics Reports*. Vol. 53, No. 9. Hyattsville, MD: National Center for Health Statistics, 2004.

[15] Niswander KR, Gordon M. *The Women and Their Pregnancies. Pub. No. (NIH) 73-379*. Washington, D.C.: U.S. Government Printing Office, U.S. Department of Health, Education, and Welfare, 1972.

[16] Kramer MS, McLean FH, Boyd ME, Usher RH. The validity of gestational age estimation by menstrual dating in term, preterm and postterm gestations. *JAMA* 1988;**260:**3306–08.

[17] Scorer CG. The descent of the testis. *Arch Dis Child* 1964;**39:**605–09.

[18] Hutson JM, Hasthorpe S. Testicular descent and cryptorchidism: the state of the art in 2004. *J Pediatr Surg* 2005;**40:**297–302.

[19] Myrianthopoulos NC, French KS. An application of the U.S. Bureau of the Census socioeconomic index to a large, diversified patient population. *Soc Sci Med* 1968;**2:**283–99.

[20] Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. *Obstet Gynecol* 1982;**59:**624–32.

[21] Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations. I. Analysis of epidemiologic factors in congenital malformations. Report from the Collaborative Perinatal project. *Birth Defects Orig Artic Ser* 1975;**11:**1–22.

[22] Abratt RP, Reddi VB, Sarembock LA. Testicular cancer and cryptorchidism. *Br J Urol* 1992;**70:**656–59.

[23] Zhang Y, Graubard BI, Klebanoff MA, Stanczyk MA, Longnecker MP, McGlynn KA. Associations of maternal and neonatal characteristics with maternal hormone levels in white and black women. Submitted, 2005.

[24] Beard CM, Melton LJ 3rd, O'Fallon WM, Noller KL, Benson RC. Cryptorchism and maternal estrogen exposure. *Am J Epidemiol* 1984;**120:**707–16.

[25] Davies TW, Williams DR, Whitaker RH. Risk factors for undescended testis. *Int J Epidemiol* 1986;**15:**197–201.

[26] Troisi R, Potischman N, Roberts J, Siiteri P, Daftary A, Sims C *et al*. Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). *Cancer Causes Control* 2003;**14:**347–55.

[27] Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity, and pregnancy estrogens. *Cancer Causes Control* 1990;**1:**119–24.

[28] Kaijser M, Jacobsen G, Granath F, Cnattingius S, Ekbom A. Maternal age, anthropometrics and pregnancy oestriol. *Paediatr Perinat Epidemiol* 2002;**16:**149–53.

[29] McGlynn KA, Graubard BI, Nam J-M, Stanczyk FZ, Longnecker MP, Klebanoff MA. Maternal hormone levels and risk of cryptorchism among populations at high and low risk of testicular germ cell tumors. *Cancer Epidemiol Biomarkers Prev* 2005;**14:**1732–37.

[30] Ekbom A, Hsieh CC, Lipworth L, Adami HO, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. *J Natl Cancer Inst* 1997;**89:**71–76.

[31] Swerdlow AJ, Wood KH, Smith PG. A case-control study of the aetiology of cryptorchidism. *J Epidemiol Community Health* 1983;**37:** 238–44.

[32] Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. *Environ Health Perspect* 1999;**107:**297–302.

[33] Bianca S, Ingegnosi C, Ettore G. Maternal age and hypospadias. *Acta Obstet Gynecol Scand* 2005;**84:**410.

[34] Fisch H, Golden RJ, Libersen GL, Hyun GS, Madsen P, New MI *et al*. Maternal age as a risk factor for hypospadias. *J Urol* 2001;**165:** 934–36.

[35] Porter MP, Faizan MK, Grady RW, Mueller BA. Hypospadias in Washington State: Maternal risk factors and prevalence trends. *Pediatrics* 2005;**115:**e495–99.